

# Ophthalmic Plastic and Reconstructive Surgery

## Lacrimal Sac Sebaceous Carcinoma

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Abstract</b></p> <p>Sebaceous carcinoma is an aggressive malignancy with a high mortality rate that commonly arises in the periorbital area. Rarely the lacrimal apparatus may be involved by either contiguous or non-contiguous spread. The authors describe two unusual cases of sebaceous carcinoma in the lacrimal sac presenting as a medial canthal mass simulating chronic dacryocystitis. In case 1, the sebaceous carcinoma occurred primarily in the lacrimal sac, in the absence of concurrent or previous ocular adnexal sebaceous neoplasia. Mapping biopsies found no evidence of intraepithelial disease. Case 2 developed a late non-contiguous disease recurrence involving the lacrimal sac five years post-primary resection of an ipsilateral eyelid sebaceous carcinoma. These cases demonstrate atypical mode of spread of sebaceous carcinoma into lacrimal excretory system. It is important to regard the nasolacrimal drainage system as a potential reservoir for neoplastic sebaceous cells and minimise the risk of tumour cell dissemination during surgical management of eyelid or conjunctival sebaceous cell tumours.</p>

## MANUSCRIPT SUBMISSION CHECKLIST

*Please review and check the items in this checklist to ensure that the submission process proceeds without unnecessary delay.*

- ☒ Every author made a significant contribution to the design or execution of the study, writing of the manuscript, or both.
- ☒ This paper is not under consideration for publication by another journal, nor is it in press in any other format.
- ☒ This paper has not been previously published in whole or in part in another publication.
- ☐ For studies involving research on human subjects or animals, a statement is included in the Methods section that Institutional Review Board (IRB) or Ethical Standards Board approval was obtained, or a waiver was granted. For research conducted at institutions or countries where IRB or Ethical Committee oversight is not available, a statement to that effect is included in the Methods section. Case Reports on 1-6 patients that do not involve a research protocol are exempt.
- ☐ For studies performed in the United States, a statement is included in the Methods section that the study was HIPAA-compliant, with protection of individually identifiable health information, unless consented by the patient. Case reports should include this statement in the article introduction.
- ☐ For all studies that are exempt from IRB or Ethical Committee oversight, a statement is included in the Methods section that the research adhered to the tenets of the Declaration of Helsinki as amended in 2008.
- ☐ For a detailed explanation regarding IRB or Ethics Committee oversight, HIPAA compliance and the appropriate use of the Declaration of Helsinki statement see [http://journals.lww.com/ops/Fulltext/2013/09000/Institutional\\_Review\\_Boards,\\_Declaration\\_of.1.aspx](http://journals.lww.com/ops/Fulltext/2013/09000/Institutional_Review_Boards,_Declaration_of.1.aspx)
- ☒ A statement that consent to publish identifiable photographs has been obtained and is archived with the authors is included in the Methods section (or the introduction of case reports).
- ☐ All clinical photographs without consent, are cropped so that patient identification is not possible.
- ☒ The manuscript adheres to the page limitations specified for each article type in the *Information for Authors*; Major Reviews-10 pages, Original Investigations-6 pages, Anatomy and Physiology and Surgical Techniques-3 pages, Case Reports-2 pages, Letters-1 page. Page calculation includes text, tables, and all figures.
- ☒ A one sentence Précis of 35 words or less is provided.
- ☒ A structured abstract including Purpose, Methods, Results, and Conclusion is included for all manuscript types, except Case Reports where an unstructured abstract is provided.
- ☒ The text of the manuscript is submitted in Microsoft Word, double-spaced, and with numbered lines.
- ☒ References follow the format specified in the *Information for Authors*, and are numbered sequentially as cited in the manuscript.
- ☐ Tables are provided on a separate page and data are consistent with those mentioned in the text.
- ☒ A separate legend is provided for each Table and Figure, and legends are submitted on a separate page.
- ☒ Tables and Figures are submitted on separate pages and not imbedded in the text of the manuscript.

- ☒ Photographs are of high resolution and not out of focus.
- ☐ For all studies involving cancer, the TNM classification scheme as defined in the 7<sup>th</sup> edition of the American Joint Commission on Cancer (AJCC, Springer, 2010) has been used.
- ☒ For all manuscript types excluding Letters to the Editor and Images in OPRS, a separate, signed copyright from each coauthor must be uploaded at the revision stage. LTEs and Images must submit separate, signed copyrights from each coauthor at the time of original submission.
- ☒ A conflict of Interest statement is provided for each author.
- ☒ All sources of funding related to this paper have been disclosed.
- ☒ A corresponding author is designated with contact information and this individual will be available at this e-mail address until publication of the paper.

## Point by point response

Dear Editor,

We would like to thank the reviewers for their very detailed and constructive feedback.

Please find below our point by point response.

Please note that the changes/additions in the text are highlighted in yellow.

### Response to Reviewer #1:

- 1) **"The tumor is referred to as sebaceous cell carcinoma in this paper. All 7 references in the bibliography and most textbooks call this malignancy sebaceous carcinoma".**

Thank you for this point - we agree - and have corrected the terminology throughout the case report to this effect.

- 2) **"As a general rule, when placing an exceptionally rare or unusual diagnosis in the literature, a certain level of "proof" is required. In the first case of primary sebaceous carcinoma the histopathology shows an undifferentiated tumor and the immunohistochemical stains for adipophilin were not adequate to interpret in grey scale."**

Thank you - we agree that the image provided was of low magnification, and therefore difficult to interpret in grey scale. We have corrected this by providing a higher magnification image of the Adipophilin stain in the tumour cells (as Figure 2D).

We have also provided images of the second case (Figure 4A-D).

Please note that the tumour cells of both cases, showed an immunohistochemical profile consistent with sebaceous carcinoma, namely: EMA+, Ber-EP4+, Adipophilin+ and Androgen receptor positive. This was not stated in the original text, but we provide an image of the AR stain in the second case.

Unfortunately, we can no longer add in micron bars into the original images, as these were taken on an old photographic system.

- 3) **In the Introduction it states "Sebaceous cell carcinoma is an aggressive malignancy with a high mortality rate....". Then 2 sentences later it reads: "It may also exhibit local invasive behavior or metastasize...". It seems unnecessary to remind the reader the tumor is also locally invasive when you just mentioned it could kill him or her.**

Thank you for the suggested alterations to the text: we have made these where appropriate.

- 4) **In Case 2 it does not mention the side that the primary eyelid sebaceous occurred on. I assume the same side as the lacrimal sac, but I would explicitly state such.**

Indeed, this was on the same side (i.e. right side). The text was changed accordingly.

### Response to Reviewer #2:

- 1) **Both cases of SGC were proven by histopathology. The first case had poor vision in the fellow eye for which globe salvaging surgery was done. Why did the authors not think of neo-adjuvant chemo therapy (NACT) described in orbital sebaceous carcinoma. A series of orbital SGC has been reported by Kaliki S et al and found good response to NACT. The down staging of the SGC by NACT may have helped globe/vision salvaging surgery in one or both cases. Authors will need to comment why they did not consider NACT?**

Thank you for highlighting this important aspect of management. We agree that NACT has shown promising results in early reports, however the role of chemotherapy has not been well defined in SGC yet. A few case reports and series existed at the time of treatment of patient 1 describing use of chemotherapy to shrink tumour mass prior to surgical excision (eg Kaliki's group 2015, 10 cases; Murthy 2005- case with regional LN mets). However, these described mostly larger tumours in younger patients than ours mostly with lymph node involvement (Naik's cases T3 n=6, N1=6, M1 n=2). The patient was discussed in skin cancer MDT and since there was no LN involvement and the tumour was resectable without NACT, the evidence for NACT was not felt

to be compelling, and after discussion with the patient the option of urgent surgical resection followed by highly focal IMRT was chosen. We have now pointed this out in the discussion section.

**2) Abstract is not structured. It will help readers if the authors provide a structured abstract highlighting the atypical mode of spread in SGC.**

We have modified the abstract to highlight the atypical mode of the spread, however the journal requirements indicate an unstructured format for case report abstracts.

**3) Case report 2 describing SGC in 85 yr old female fails to mention the duration of follow-up.**

Duration of follow-up is three years for case 2. Also patient 1 follow-up duration was updated in the text (now 2.5 years post-op).

**4) Both cases do not mention the TNM staging as per AJCC.**

TNM staging was added to both according to AJCC eight edition for eyelid cancers and the reference section was updated accordingly.

**Response to Reviewer #3:**

**1) For the case no 2, please mention the follow up duration.**

Duration of follow-up is three years for case 2. This is now mentioned in the text.

**2) For the case no 1, since the follow up is for 2 years, it would be great to have a post op picture in the collage.**

We have now included a photo (Figure 1E) from most recent follow-up (2.5 years post-op)

**3) Please mention a line about the possible plan for lacrimal rehabilitation in the patient no 1.**

In terms of lacrimal rehabilitation, patient number 1 underwent successful insertion of Lester Jones tube. This is now highlighted in the text.

We would like to thank the Reviewers again for their suggestions, which has led to an improvement in the manuscript.

With kind regards,

Dr Kaveh Vahdani (on behalf of my co-authors).

## **Precis**

We describe two rare cases sebaceous carcinoma in the lacrimal sac presenting as a medial canthal mass simulating chronic dacryocystitis.

## **Abstract**

Sebaceous carcinoma is an aggressive malignancy with a high mortality rate that commonly arises in the periorbital area. Rarely the lacrimal apparatus may be involved by either contiguous or non-contiguous spread. The authors describe two unusual cases of sebaceous carcinoma in the lacrimal sac presenting as a medial canthal mass simulating chronic dacryocystitis. In case 1, the sebaceous carcinoma occurred primarily in the lacrimal sac, in the absence of concurrent or previous ocular adnexal sebaceous neoplasia. Mapping biopsies found no evidence of intraepithelial disease. Case 2 developed a late non-contiguous disease recurrence involving the lacrimal sac five years post-primary resection of an ipsilateral eyelid sebaceous carcinoma. These cases demonstrate atypical mode of spread of sebaceous carcinoma into lacrimal excretory system. It is important to regard the nasolacrimal drainage system as a potential reservoir for neoplastic sebaceous cells and minimise the risk of tumour cell dissemination during surgical management of eyelid or conjunctival sebaceous cell tumours.

# Lacrimal Sac Sebaceous Carcinoma

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**Declaration:** None of the authors has a financial interest or other conflicts of interest.

**Archival statement of permission to print identifiable photo:** Consent has been obtained from the patient for publication of the medical photography included in the article.

**Key Words:** sebaceous carcinoma, sebaceous gland carcinoma, lacrimal sac tumour, chronic dacryocystitis

**Running head:** Sebaceous carcinoma of the lacrimal sac



24 **Précis**

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## **Abstract**

Sebaceous carcinoma is an aggressive malignancy with a high mortality rate that commonly arises in the periorbital area. Rarely the lacrimal apparatus may be involved by either contiguous or non-contiguous spread. The authors describe two unusual cases of sebaceous carcinoma in the lacrimal sac presenting as a medial canthal mass simulating chronic dacryocystitis. In case 1, the sebaceous carcinoma occurred primarily in the lacrimal sac, in the absence of concurrent or previous ocular adnexal sebaceous neoplasia. Mapping biopsies found no evidence of intraepithelial disease. Case 2 developed a late non-contiguous disease recurrence involving the lacrimal sac five years post-primary resection of an ipsilateral eyelid sebaceous carcinoma. These cases demonstrate atypical mode of spread of sebaceous carcinoma into lacrimal excretory system. It is important to regard the nasolacrimal drainage system as a potential reservoir for neoplastic sebaceous cells and minimise the risk of tumour cell dissemination during surgical management of eyelid or conjunctival sebaceous cell tumours.

## **MAIN TEXT**

### **Introduction**

Sebaceous carcinoma is an aggressive malignancy with a high mortality rate that commonly arises in the periorbital area, usually in the eyelid. The tumour is well known for mimicking other periocular lesions, often leading to delayed diagnosis or misdiagnosis. [1-6] The authors describe two unusual cases of sebaceous carcinoma in the lacrimal sac, presenting as a medial canthal mass simulating chronic dacryocystitis. Patient consent has been obtained for publication of the medical photography included in the article. This report adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013.

### **Case 1**

A 74-year-old woman was referred with a one-year history of right epiphora followed by a firm, non-tender swelling at the right medial canthus present for 6 months [Fig 1 A] and mimicking a chronic dacryocystitis. Imaging of orbits/sinuses with contrast demonstrated an enhancing mass within the medial aspect of the right orbit centered on the lacrimal sac, displacing the globe laterally with extension into the nasolacrimal duct, with obstruction of the frontal sinus drainage and osteomeatal complex. [Fig 1 B-C] Incisional biopsy of the lacrimal sac mass revealed a poorly differentiated carcinoma composed of small-to-medium sized cells with oval nuclei, prominent nucleoli and foamy cytoplasm. On immunohistochemistry, the cells demonstrated positivity for epithelial membrane antigen (EMA), Ber-EP4, and focally for adipophilin. [Fig 2] On the basis of the morphological and immunohistochemical findings, the diagnosis of sebaceous

carcinoma was made. [Fig 2] Conjunctival mapping biopsies did not identify pagetoid intraepithelial disease. Based on American Joint Committee on Cancer (AJCC) eighth edition<sup>8</sup> the staging of the tumour was: T4bN0cM0. Following a multidisciplinary team discussion, the option of potentially curative exenteration with ethmoidectomy and maxillectomy was proposed; however, due to poor vision in the contralateral eye (OS = 1/60 caused by previous central retinal vein occlusion), it was decided to perform a globe-sparing surgical de-bulking of the tumour with adjuvant radiotherapy to medial orbit and maxilla.

Intraoperatively, the globe was found to be separate from the tumour that appeared to have been resected *in toto*. Post-operatively, vision and eye motility have been preserved at 2.5 years follow-up with no evidence of local or distant recurrence. (Fig 1E). She also underwent successful lacrimal bypass tube surgery (Lester Jones tube) for lacrimal rehabilitation.

## Case 2

An 85-year-old woman was referred with a right medial canthal mass and epiphora. She had previous local resection of a small right upper eyelid sebaceous cell carcinoma five years prior at a different unit. CT images demonstrated a soft tissue mass within the right lacrimal sac, which extended into the nasolacrimal duct but without post-septal extension. MRI scan also illustrated an enhancing soft tissue mass within the right lacrimal sac. The mass appeared separate from the extraocular muscles and there was no extension into the orbital fat. [Fig3] MRI neck, chest, abdomen and pelvis did not find evidence of metastatic disease.

Incisional biopsy of the lacrimal sac lesion diagnosed a sebaceous cell carcinoma, on the basis of morphological and immunohistochemical (EMA+, Ber-EP4+, Adipophilin+ and androgen receptor+) findings. [Fig4] Conjunctival mapping biopsies excluded intraepithelial spread or invasive sebaceous cell carcinoma. (AJCC staging T4bN0cM0) Subsequently, the patient underwent orbital exenteration with adjuvant radiotherapy. Post-operatively she developed recurrent wound infections requiring hospitalisation and intravenous antibiotics. Further CT orbits demonstrated a persistent fistula from the ethmoid sinus following exenteration, which required surgical repair with a local advancement flap. Three years postoperatively, there has been no evidence or recurrent disease.

## DISCUSSION

Sebaceous carcinomas derived from neoplastic cells of sebaceous glands, most commonly located within the meibomian glands of the tarsus, but also potentially from Zeis glands, caruncle, pilo-sebaceous units within the eyebrow skin. Eyelid sebaceous carcinoma may spread locally by invading the adjacent epithelia or the orbital soft tissues, lacrimal secretory apparatus or cranial cavity in advanced cases. [1] New immunohistochemical markers on fixed material (e.g. adipophilin) aid the diagnosis of sebaceous carcinoma [7].

Involvement of the lacrimal excretory system by contiguous spread is rare. Margo et al. reported a case of widespread intraepithelial sebaceous carcinoma of the conjunctiva and skin of the eyelid with contiguous extension into the introitus of the lower canaliculus. [4]

Khan et al. discovered pagetoid canalicular involvement in three cases in which the canaliculus was excised at the time of the surgery. They also found prelacrimal tumour spread to the nasolacrimal duct with tumour mass in the inferior turbinate in another case. [5]. All these cases had documented intraepithelial conjunctival or cutaneous spread, in contrast to our cases.

Rath et al. described a case of sebaceous carcinoma of the eyelid metastasizing to the ipsilateral lacrimal sac five years after complete primary excision. No mapping biopsies were performed at the time of the primary surgery. Imaging showed a mass in the lacrimal sac with bony erosion. Histopathology confirmed sebaceous carcinoma of the lacrimal sac but no infiltration of the nasolacrimal duct or conjunctiva were identified. [6] Literature review did not detect any previous cases of sebaceous carcinoma primarily arising in the lacrimal sac.

The mechanism of tumour spread into the lacrimal outflow system is uncertain. Two patterns have been postulated. Relatively contiguous tumours are believed to follow a pagetoid intraepithelial dissemination route. Whereas, widely separated non-contiguous areas of tumour involvement may suggest free-floating tumour cells are carried in the tears (so-called oncorrhoea) and seeded in the lacrimal drainage system via the canalicular aqueous flow. This implantation via tear film may also account for the non-contiguous conjunctival multicentric lesions or skip lesions. A combination of both mechanisms may also be accountable. [1, 5]

Both our cases had rather unusual presentations with unclear mechanism of tumour cell spread. In case 1, the invasive tumour occurred primarily in the lacrimal sac, which is devoid of sebaceous glands. This patient had no previous history of eyelid or adnexal malignancy nor any evidence of intraepithelial disease on mapping biopsies. A hypothetical explanation could be the presence of an ectopic (choristomatous) sebaceous gland [4] within the lacrimal sac, leading to a subsequent malignant transformation. It has been suggested that extraorbital sebaceous cell carcinoma involving the parotid gland may arise from pluripotent or ectopic cells retained during embryological development. [1] Another hypothesis is sebaceous gland metaplasia of the lacrimal sac epithelium with subsequent malignant transformation. However, it is extremely difficult to prove any of these theories. A further possibility is the presence of a previous small occult tumour resulting in distal implantation of free-floating cancer cells via the tear film.

Case 2 developed a late non-contiguous disease recurrence involving the lacrimal sac five years post-primary resection, similar to one described by Rath et al. [6] Our case additionally exhibited an extension of tumour into the nasolacrimal duct. Mapping biopsies did not show any evidence of pagetoid spread. We presume that malignant cells were transported by tears and implanted in the lacrimal sac, as previously suggested in the literature. [5, 6] The delayed involvement of the lacrimal sac in this case diminishes the likelihood of a multicentric synchronous disease.

Wide local excision with margin control or Mohs micrographic surgery represent the mainstay of management. [9,10] Chemotherapy and radiotherapy may also be useful in

recurrent or metastatic disease. Although the field is evolving, the role of chemotherapy has not been well defined in sebaceous carcinoma. Previous reports have described the utility of neoadjuvant chemotherapy (NACT) by downstaging the sebaceous carcinoma and aiding globe salvaging surgery, however these mainly included younger patients with mostly lymph node metastasis. [11,12]. The management of case 1 in our study was discussed in skin cancer multidisciplinary team and since there was no lymph node involvement and the tumour was considered resectable without NACT, as well as the paucity of evidence for NACT, the option of urgent surgical resection followed by highly focal Intensity-modulated radiation therapy (IMRT) was agreed, following discussion with the patient.

Our cases demonstrate the notorious diverse presentation of sebaceous carcinoma, and the importance of close clinicopathological correlation. The first case presented as a primary sac tumour in the absence of concurrent or previous ocular adnexal sebaceous neoplasia. The importance of urgent imaging and biopsy of suspicious medial canthal masses is paramount. Regular and long-term follow-up is vital as recurrence or metastatic disease can occur many years after primary surgery. It is also important to regard the nasolacrimal drainage system as a potential reservoir for neoplastic sebaceous cells and minimise the risk of tumour cell dissemination during surgical management of eyelid or conjunctival sebaceous cell tumours. [1]



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## LEGENDS

**Figure 1.** (A) Medial canthal mass masquerading as chronic dacryocystitis. (B) axial and (C) coronal CT illustrate a right lacrimal mass invading the medial orbit, ethmoidal sinus and nasolacrimal duct (D) T2-weighted MRI demonstrates a fairly homogeneous mass in the lacrimal sac. (E) Clinical appearance at 2.5 years follow-up with no evidence of recurrence.

**Figure 2.** A) Histopathological sections revealed a poorly-differentiated carcinoma, completing filling the lacrimal sac and invading into the adjacent stroma (Haematoxylin and Eosin (H&E), x 10 objective). B) On higher power, the foamy cytoplasm of the pleomorphic cells can be seen (H&E stain, x 20 objective). C) Adipophilin stain demonstrates focal positivity of this marker within the cytoplasm of some of the cells (DAB, x20 objective) Square box highlights area of higher magnification in image D). D)

Patchy adipophilin positivity in sebaceous carcinoma cells with clear negativity seen in the adjacent lymphocytic infiltrate (DAB, x40 objective).

**Figure 3.** ( A) Axial and(B) Coronal CT show soft tissue in the lacrimal sac extending into superior part of the nasolacrimal duct, (C) enhancement of the mass in post-gadolinium T2 weighted MRI.

**Figure 4.** (A) Histological section stained with Haematoxylin and Eosin of the incision biopsy of the lacrimal sac mass demonstrated a moderate to poorly-differentiated invasive tumour occurring in nests as well as single cells, separated by fibrotic bands, and showing a brisk mitotic count (H&E, objective 20x).

(B) Strong membranous positivity of the tumour cells for Ber-EP4 (DAB, objective 40x).

(C) Globular positivity of adipophilin in the cytoplasm of the carcinoma cells, which also extend into the surgical resection margin (DAB, objective 60x). (D) Nuclear positivity of the tumour cells for androgen receptor in a better differentiated region of the tumour (DAB, objective 40x).







